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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/565,322
Filing Date: January 20, 2006
Appellant(s): KARAVAS ET AL.

Aliki K. Collins
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 10-6-2010 appealing from the Office action mailed 04/15/2010

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The statement of the status of amendments contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 641,885,8	Sherman et al.	07-2002
US 669,649,6	Oosterbaan et al.	02-2004
US 2002/0155156	Muyle et al.	10-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherman et al (US 6419958) in view of Oosterbaan et al. (US 6696496) further in view of Mulye (US 2002/0155156)

Sherman et al teaches a 24 hour extended release dosage formulation and unit dosage form of venlafaxine hydrochloride, which provides better control of blood plasma levels that conventional tablet formulation which are administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets (abstract). Sherman teaches that extended release capsule dosage form comprising film coated spheroids are placed in pharmaceutically acceptable capsules such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect and the spheroids releasing the drug at different rates may be

combined in a capsule to obtain desired release rates and blood levels (co..1, lines 40-54). Sherman's formulation comprises an extended release formulation of venlafaxine hydrochloride in the form of spheroids comprising a therapeutically effective amount of venlafaxine hydrochloride, microcrystalline cellulose and optionally hydroxypropylmethyl cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose (col.2, line 65 to col.3, line 5). Sherman teaches that his extended release formulation compromise about 6-40% venlafaxine, preferably between 30-40% and optionally from about 0.225% to 1% by weight of hydroxypropylmethyl cellulose (col.3, lines 10 and line 20-25). Sherman additionally teaches that his drug is film coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about 2-12% on the wt/wt basis of the final product (col.4, lines 13-17). Sherman teaches that other equivalents of the hydroxypropylmethyl cellulose and ethyl cellulose having the same physical and chemical characteristics may be substituted in his formulation (col.4, line 44-47). Sherman also teaches the use of binders such as polyvinylpyrrolidone in his formulation (col.5, 4-5).

Sherman does not teach the controlled release formulation of Venlafaxine hydrochloride in the form of mini-tablets, and the coating composition comprising the polymer and the water-soluble component.

Oosterbaan teaches low water soluble salts of venlafaxine in a variety of dosage forms including hydrogel-based extended release dosage forms (abstract). Oosterbaan teaches oral dosage forms of venlafaxine maleate which includes tablets, capsules, powders etc. including hard gelatin capsules that can be filled with powder, pellets,

granules, small tablets or mini tablets and the capsule or the material place within can be coated for enteric or modified release (col.7, lines 29-42). Oosterbaan teaches that the most desired dosage form is the extended release dosage form (col.7, lines 47-48). Oosterbaan teaches that pharmaceutically acceptable excipients are well known in the art and include diluents, fillers, binders, lubricants, disintegrants, glidants, colorants, pigments, taste masking agents, sweeteners, plasticizers, and any acceptable auxiliary substances such as absorption enhancers, penetration enhancers, surfactants, co-surfactants, and specialized oils. The proper excipient(s) are selected based in part on the dosage form, the intended mode of administration, the intended release rate, and manufacturing reliability (col.6, lines 50-59). Oosterbaan teaches hydrophilic matrix material in extended release matrix tablet to comprising a polymeric material that swells upon contact with water and exemplifies hydroxypropylmethylcellulose (HPMC) among others (col.8, lines 50-54) and additionally teaches inert matrix material which provides a tortuous path for the drug to escape the dosage form thereby controlling diffusion of the drug and exemplifies ethylcellulose (ETHOCEL) (col.8, lines 61-64). Oosterbaan teaches that the hydrogel tablet of his invention comprises 10-50% of venlafaxine maleate and 30-75% of the hydrogel-forming agent, preferably an HPMC (hydroxypropylmethyl cellulose) and the composition may further comprised other inert ingredients such as fillers, lubricants etc (col. 9, lines 21-35) Oosterbaan also teaches the tablets to be prepared according to any standard tabletting technique, e.g. wet granulation, dry granulation or direct compression (col.9, lines 37-41). Oosterbaan further teaches the mini-tablets to be one of the preferred embodiments of his invention

which have a diameter of 1-3 mm and one or more of the tablets preferably loaded into a single capsule to provide a unit dose. Oosterbaan teaches that the small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile which is not as easily obtained with a proportionally larger hydrogel tablet (col.9, lines 52-59 and 65). Oosterbaan teaches the release to be a function of the volume to surface area ratio, and accordingly scaling up the amount and size of a satisfactory 37.5 mg tablet to 150 mg tablet will likely not result in a satisfactory release profile, because the volume to surface area ratio is different between the two tablets. As a consequence of which for each desired single dosage level, a separate formulation, size and/or shape would be needed. However by using small or mini tablets in a single capsule, only one tablet formulation and shape is needed to produce multiple dosage strengths and typically a small or mini-tablet containing 5 to 50 mg of venlafaxine maleate .Depending on the size of the tablet and the capsule, from 1 to 10 or more small or mini-tablets can be placed in the capsule (col 9, line 66 to col.10 line 14). Oosterbaan additionally teaches that in addition to filling capsules with small or mini-tablets, an extended release capsule can be formed by filling it with more traditional pellets, beads, and/or spheres. Oosterbaan does not teach venlafaxine hydrochloride as his active ingredient, but instead teaches venlafaxine maleate. However, the reason Oosterbaan provides for replacing the hydrochloride version with the maleate version is to avoid irritations of Venlafaxine HCl and aggressiveness of the hydrochloride version on the equipment, Oosterbaan however teaches that venlafaxine hydrochloride provides good pharmaceutical activity (col.2, lines 45-50). As such, the final dosage forms such

as tablets, capsules, extended release tablets, and hard gelatin capsules comprising beads/spheroids or mini-tablets are forms which can be utilized for any pharmaceutical agent with the appropriate excipients and is not necessarily confined to the venlafaxine maleate only. Accordingly, Oosterbaan provides an ordinarily skilled artisan motivation to develop extended release formulation comprising venlafaxine hydrochloride in dosage forms other than the spheroids such as mini-tablets.

Mulye teaches coating composition for coating a solid dosage form of the medicament directed to a system for the controlled release formulation (abstract). Mulye's coating formulation can be used to coat various cores that contain tablets, spheroids, micro spheres, seeds, pellets, or other multi-particulate systems to achieve a controlled release of the main ingredient longer than 24 hours [0040]. Muyle also teaches that the first component of the coating is the water insoluble polymer ([0045], lines 1-2) and lists Eudragit RS ® and Eudragit RL® [0048] as suitable choices. Mulye teaches that the insoluble polymer more preferably comprises at least 60% by dry weight of the coating material [0052]. Mulye further states that the second component of the coating is a water soluble compound ([0054], lines 1-2) such as lactose or sucrose, propylene glycol, sugar alcohols, polydextrose etc. [0055] and preferably makes up 20-30% of the coating [0060] . In examples 1, 2 and 5, Mulye teaches the polymer: water soluble component ratio used in the coating process to be 4:1, 3: 1 and 9:1 respectively [0012] - [0117] reference claims 2 and 9-10). According to Mulye, the amount of coating applied is sufficient to retard the release of the active component at a desired rate, therefore the coating composition is applied to the core in a thickness sufficient to obtain

the desired release profile of a therapeutically active agent when the coated substrate is exposed to aqueous solutions and Mulye prefers the coating composition of his invention to be applied to the core at a thickness ranging from about 1% to about 15% by dry weight of the composition more preferably from about 3 to about 6% of the composition ([0089], reference claims 24--26). Mulye additionally teaches the coating compositions to comprise of other additives normally found in coatings used in the pharmaceutical arts such as plasticizers ([0066] and reference claim 14), wetting agents, lubricants, coloring agents [0065], masking agents and the like [0063]. Mulye also teaches the method of preparation of the coating which is by art recognized techniques which includes dispersion of the polymer and the water soluble compound in pharmaceutically acceptable solvent such as water [0068]. Muyle teaches the coating composition of his invention is coated onto the core containing a drug in any conventional oral unit dosage form, such as a tablet, capsule, pill, granule or powder to form the desired preparation where in the coating composition coats the central core element utilizing conventional methods known in the art such as using a fluidized bed or pan; spraying or painting the suspension of the composition onto the formulation; or using a fluid bed bottom spray coater [0083]. Muyle teaches that the coating forms films around the core and the strength of the film is dependent on the presence of water insoluble polymer and the water soluble component [0091]. Finally Muyle teaches advantages to using his coating compositions to coat controlled release formulation as follows: (1) it is completely aqueous; there is an avoidance of organic solvents, which have inherent safety concerns, inflammability, carcinogenicity, environmental concerns

costs, safety in general. It is also very simple to make. (2)The uniformly dispersed component allows uniform wetting of the coat, it yields better uniformity of dry release between tablet and allows for better adhesion to the water wettable core (3) The coat is wettable. (4) The rate of release can be controlled by controlling the porosity of the coat or the thickness of the coat ([0093]-[0099]). Muyle teaches sustained release formulations comprising any one of the active ingredients at concentrations of 0.5-90% [0070-0071] comprising fillers such as lactose preferably at 30-40% [0073], binders which helps promote adhesion of the drug to the beads preferably at concentrations of 3-15% exemplified by polyvinylpyrrolidone [0077-0078] and sellable polymers such as hydroxypropylmethylcellulose at concentrations of 2-20% wt based on the weight of the core [0081-0082].

With regards to the new limitation in the amended claim 1 "once a day" preparation, Sherman et al. teaches that the use of the once-a-day extended release venlafaxine hydrochloride formulations and further teaches the advantages of such a dosing in that it reduces by adaptation, the level of nausea and incidence of emesis that is associated with multiple daily dosing of venlafaxine HCl (col.2, lines 48-64). Oosterbaan et al. teaches a hydrogel tablet of venlafaxine maleate which provides sufficient extended release so that the tablet is a once daily form (col.3, lines 7-16 and col.7, line 61 to col.8, line 7)). With regards to the new limitation in the amended claim 1 "wherein the functional coating layer or coating film limits the initial rapid diffusion of the drug substance from the functional cores", Mulye explicitly teaches a coating composition identical to that which is instantly claimed with a polymer and a water-

soluble component in which the release rate of the drug can be controlled by varying the thickness of the coating on the mini-tablets. In addition Mulye teaches that the low molecular weight component in his inventive coating composition, prevent rapid movement of water through the coat because of its uniformly dispersed component which allows uniform wetting of the coat and allows better adhesion to the water wettable core [0094-0096]. As such, utilizing the coating formulation taught by Mulye, for sustained release of a drug, an ordinarily skilled artisan would essentially have a composition which limits the rapid water diffusion across the coating which consequently prevents initial rapid diffusion of the drug substance from the functional cores. Furthermore, drug release from a coated sustained release composition is a functional limitation of the coating compositions and the composition of the core of the dosage form. Since Mulye teaches the instantly claimed coating composition, accordingly, the composition of Mulye will inherently possess the functional limitations set forth in the instant application. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the appellants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph

With regards to instant claims 2 and 5 which recites the use of a conjugation agent. Binding agents taught by Sherman and Muyle such as polyvinylpyrrolidone reads

on the conjugation agent. Conjugation agent is recited in the instant disclosure as an agent which forms a bond between the swellable and non-swellable polymer and could be surfactant or a polymer and examples of the polymer include 'polyvinylpyrrolidone' (instant disclosure, page 5, section iv). As such polyvinylpyrrolidone taught as binding agent by both Sherman and Muyle reads on this limitation. As suggested by the appellant in the disclosure, surfactants such as sodium lauryl sulphate and the polymer such as poly vinylpyrrolidone with reference to controlled release formulation are functional equivalents and both provide binding of the swellable and non-swellable polymers. As such use of such a binder in the pharmaceutical arts for the formulation of controlled release dosage forms is well known and an ordinary skilled artisan would have been motivated to use a binding agent as taught by Sherman and Muyle in the development of a venlafaxine hydrochloride tablet.

With regards to instant claim 6, Mulye teaches coating composition of his invention to be applied to the core at a thickness ranging more preferably from about 3 to about 6% of the composition [0089] and with reference to the partial coating of the cores, although Mulye does not specifically teach partial coating, since the coating composition and method taught by Mulye is the same as instantly claimed, it would be obvious to an ordinarily skilled artisan to develop different ways of coating the core with different thickness of the coating based on the required drug release profile.

With regards to instant claim 17, Mulye teaches that it is critical in his coating compositions that the soluble component is substantially and more preferably

completely soluble in the coating dispersion and upon formation of the coat, the soluble component is uniformly dispersed in the coating composition [0062].

With regards to the instant claim 22, which recites the limitation that the mini-tablets are partially or totally coated by a coating layer or coating film that is functional only during the first 2-4 hours of the drug release, as taught by Muyle, who incidentally explicitly teaches a coating composition identical to that which is instantly claimed with a polymer and a water-soluble component, the release rate of the drug can be controlled by varying the thickness of the coating on the mini-tablets. Muyle provides motivation to one of ordinary skill in the art to utilize the coating composition of his invention since it provides the advantage of uniform thickness and by varying the thickness of the coatings the drug release rate can be altered and it would be obvious to one of ordinary skill in the art to test formulations with varying coating thickness to arrive at the instantly claimed release rate.

With regards to instant claim 20, which recites the limitation where in the linearity between the total weight of the mini-tablets and the strength of the said dosage form is achieved. One of ordinary skill in the art can easily conceive a controlled release tablet with such a feature given the teachings of Oosterbaan. Oosterbaan teaches that the small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile which is not as easily obtained with a proportionally larger hydrogel tablet and by using small or mini tablets in a single capsule, only one tablet formulation and shape is needed to produce multiple dosage strengths and typically a small or mini-tablet containing 5 to 50 mg of venlafaxine maleate .As such one of

ordinary skill in the art can easily envisage dosage forms of multiple strengths each comprising a different number of mini-tablets within a capsule thereby achieving a clear linear relationship between the total weight of the mini-tablets with the strength of the said dosage form.

With regards to the limitation in instant claim 21, which recites that "the dose may be divided by reducing the number of tablets in the capsule, Oosterbaan teaches the mini-tablets one of the preferred embodiments of his invention where in one or more of the tablets are preferably loaded into a single capsule to provide a unit dose. Oosterbaan teaches that the small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile and teaches capsules containing 1 , 2 or 4 of the small tablets which corresponds to 37.5 mg, 75 ,g and 150 mg venlafaxine maleate dosage forms (col.9, lines 52-59 and 65)

In view of the foregoing references, the instantly claimed pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCL in the form of hard gelatin capsule containing coated mini-tablets would have also been prima facia obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Muyle in combination with Sherman and Oosterbaan. Controlled release dosage form is a well established art in pharmaceutical sciences and the various excipients such as gelling agents, non-swelling polymer, conjugation agent and coating formulations comprising a polymer and a water soluble component were known in the art at the time of the invention. Delivery of Venlafaxine hydrochloride in the controlled release form such as spheroids filled into capsules is well

established as taught by Sherman., Oosterbaan provides an ordinarily skilled artisan teachings of delivery of venlafaxine salt albeit a different salt than hydrochloride in different dosage forms which includes the instantly claimed mini-tablet forms and the spheroids forms which are filled into hard gelatin capsules. As such use of Mini-tablets in a capsule as one of the controlled release dosage form was well known at the time of the invention as evidenced by Oosterbaan. An ordinarily skilled artisan would therefore be motivated to develop a dosage form in the form of mini-tablets as opposed to the spherule form of controlled release Venlafaxine hydrochloride dosage form taught by Sherman given the advantages of being able to deliver multiple strength dosages by preparing just one form of the drug as taught by Oosterbaan. Coating of tablets in pharmaceutical sciences to establish controlled delivery of the drug is also well established art in pharmaceutical sciences. Muyle provides one of ordinary skill in the art motivation to utilize his method of coating tablets to achieve controlled release as it offers several advantages over other methods such as increased safety, reduced costs, uniformity of coating which provides improved adhesion, ability to control the release by varying the thickness etc. As such one of ordinary skill in the art would be motivated to utilize the more advantageous method of coating tablets as taught by Muyle to coat venlafaxine hydrochloride mini-tablets formulated by combining the teachings of Sherman and Oosterbaan. The advantages of such a coating procedure as recited by Muyle would provide an ordinary skilled artisan a reasonable expectation of success that such a coating would provide for a better formulated dosage form with a well controlled release of the active drug.

(10) Response to Argument

Appellant traverses the instant rejection under 35 U.S.C. 103(a), stating that the combination of Sherman et al, with Oosterbaan et al, and with Mulye does not disclose all the limitations of claims and 23 and does not make obvious the pharmaceutical formulation of the instant claim 1 and the method of instant claim 23. Specifically, appellants argue as follows:

A. The suggested combination does not disclose the limitation of claims 1 and 23 relating to the production of "mini-tablets" of the extended release formulation of water-soluble Venlafaxine HCL with the functional core that comprises an extended release formulation of the water-soluble drug substance Venlafaxine-HCl, the cited prior art teaches away from producing "mini-tablets of the extended release formulation of water-soluble Venlafaxine HCl and the cited prior art reference do not teach the limitation that "each mini-tablet comprises a functional core and the functional coating layer or functional coating film and wherein the functional core is produced with compression technology (i.e., hydrogel) and comprises an extended release formulation of the water -soluble drug substance venlafaxine HCl.

With regards to the above traversal A, appellants further argue that, Sherman et al. does not teach the controlled release formulation of Venlafaxine HCl in the form of mini-tablets but teaches the formulation in the form of spheroids, it is difficult to formulate Venlafaxine HCl in extended release tablets due to its high water solubility

and several attempts to produce extended release tablets have failed, Oosterbaan et al. is limited only to low-water soluble venlafaxine salts and that Mulye fails to mention mini-tablets of an extended release formulation of the water soluble drug substance venlafaxine HCl. Appellants argue that Sherman teaches producing spheroids of Venlafaxine HCl via extrusion and spheronization, Oosterbaan teaches a hydrogel-based process, but the process is applied only to low water-soluble Venlafaxine salts, and Mulye teaches general coating of a solid dosage form of a medicament in order to produce controlled release of an active ingredient and does not mention producing mini-tablets of the water soluble Venlafaxine HCl with compression technology,

B. The suggested combination does not make obvious the use of "a functional coating layer of functional coating film that coats the functional core and limits the initial rapid diffusion of the water-soluble drug substance from the functional core" and none of the cited art reference mentions the problem and need to limit the initial rapid diffusion of the water-soluble substance from the functional core.

With regards to the argument B above, Appellants further argue that Sherman does not utilize or rely on functional coating to produce a spheroid of an extended release formulation of Venlafaxine HCl and does not mention the problem or need to limit the initial rapid diffusion of the water soluble Venlafaxine HCl from the spheroids, Oosterbaan et al. does not teach coating the Venlafaxine salt tablets with the functional coating or mention the problem or need to limit the initial rapid diffusion of the water soluble Venlafaxine salts and finally Mulye although teaches the general method of

coating a solid dosage form for controlled release, does not mention the problem or need to limit the initial rapid diffusion of the water –soluble Venlafaxine HCl.,

Appellant's traversal arguments stated above has been fully and carefully considered, but fails to be persuasive.

First, it should be noted that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. Appellant is further reminded that the obviousness rejection is not an anticipation rejection. The above mentioned references clearly teach the advantages of development of Venlafaxine HCl. formulation as an once-a-day sustained release dosage form as it reduces side-effects associated with the drug (Sherman et al.), teaches the sustained release form can be formulated either as spheroids, mini-tablets, granules etc (Oosterbaan et al.) and teaches the application of a functional coating which increased safety, reduced costs, uniformity of coating which provides improved adhesion, ability to control the release by varying the thickness (Mulye). In obviousness rejection a combination of references is used, and the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. Appellant's claimed invention fails to patentably distinguish over the state of the art represented by the combination of the cited references. *In re Young*, 403 F.2d 754, 159 USPQ 725(CCPA 1968); *In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).*

With regards to Appellants arguments A, above, the examiner finds the arguments unpersuasive because both Sherman and Oosterbaan are not referring to the inability to make once-a -day formulations using venlafaxine hydrochloride coated mini-tablets, Rather, Sherman discloses the difficulties associated with making a 24-hour extended release venlafaxine hydrochloride tablets in general **without coatings** and teach that their encapsulated venlafaxine hydrochloride in **coated spheroids** provides a method to eliminate the problems induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. No where is Sherman or Oosterbaan specifically teaching the difficulties associated with making extended release **venlafaxine hydrochloride coated mini-tablets** or disclosing that it is impossible to make them. It appears that the Appellant has associated the difficulties of making uncoated extended release formulations prior to Sherman as the inability to make extended release formulations and has leaped to the conclusion that this encompasses extended release coated mini-tablets, Sherman, has overcome the difficulties associated with venlafaxine hydrochloride extended release formulations by providing coated formulations unlike the uncoated tablets of the past. Sherman clearly teaches a 24-hour extended release formulation of venlafaxine hydrochloride comprising coated spheroids.

Furthermore, in response to Appellants argument that the core of Sherman is in the form of spheroids, while the core of the present invention is in the form of mini-tablets and the formulation of the present invention involves procedures compression as compared to the steps of extrusion and spheronization mentioned for preparation of

spheroids in Sherman, examiner first notes that Sherman teaches Spheroids comprising 6-40% venlafaxine hydrochloride, which is very close to the range of 10-40% venlafaxine hydrochloride recited in instant claim 2. According to MPEP 2144.05, a prima facia case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough for one skilled in the art would have expected them to have the same properties, *Titanium Metals Corp. of America v. Banner, 778 F.2nd 775, 227 USPQ 773 (Fed. Cir. 1985).* Secondly, the formulation of the spheroids of Sherman comprises excipients similar to that instantly claimed such as hydroxypropylmethyl cellulose and is further coated with a mixture of ethyl cellulose and hyroxypropylmethyl cellulose to provide the desired level of coating similar to that instantly claimed. Finally, it is noted that the instant claim 1 is not drawn to formulations that are not extruded or spheronized and that since mini-tablets are not defined in the appellant's specification, there is nothing that distinguishes the instant mini-tablets from reading on the spheroids of Sherman.

The examiner disagrees with appellant that Oosterbaan and Sherman is teaching away from the use of venlafaxine hydrochloride in dosage forms comprising mini-tablets. Although Oosterbaan teaches that the low water-soluble salts of its invention are easier to formulate than venlafaxine hydrochloride, the teachings of Oosterbaan do not indicate that venlafaxine hydrochloride cannot be formulated accordingly as taught in Oosterbaan. Oosterbaan is only teaching that venlafaxine maleate is easier to formulate into conventional extended release forms. Thus, even though Oosterbaan teaches that venlafaxine hydrochloride is inferior to venlafaxine maleate in extended

release dosage forms, such as dosage forms with mini-tablets; it does not mean that the use of venlafaxine hydrochloride in dosage forms comprising mini-tablets is non-obvious. According to MPEP 2123, "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).* Furthermore, the examiner argues that Sherman clearly teaches an extended release formulation comprising venlafaxine hydrochloride, which is evidence that venlafaxine hydrochloride can be formulated into extended release dosage forms even it is associated with difficulties, as stated in Oosterbaan. Moreover, the examiner points out that Oosterbaan even references Sherman in its disclosure for its teaching of a preferred capsule of the pellet type (column 10, lines 23-28). Sherman or Oosterbaan do not explicitly criticize, discredit, or otherwise discourage compressed formulations of venlafaxine hydrochloride which are coated. Furthermore, the examiner notes that Sherman teaches problems in making formulations that are extruded in its background section (see column 5, lines 1-13). However, Sherman ultimately makes its formulations by extrusion and spheronization in its examples. Is applicant also suggesting that Sherman teaches away from extrusion? It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does

not criticize, discredit, or otherwise discourage the solution claimed…." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

With regards to applicant's argument B above, Examiner notes that Muyle et al was brought into the rejection for his general teachings of coating compositions for coating a solid dosage form of controlled release formulation. Muyle provides specific advantages of using his coating procedure for controlled release formulation and nowhere in the reference does Muyle teach an ordinarily skilled artisan not to use such a coating procedure for Venlafaxine HCl controlled release mini-tablets. As such it is the position of the examiner that Muyle provides an ordinarily skilled artisan ample teachings of coating an extended release tablet which the skilled artisan could apply to the extended release mini-tablets formulated from the combination of teachings of Sherman and Oosterbaan. Applicants argue that Muyle fails to suggest the use of their disclosed coating in order to limit the initial rapid diffusion of Venlafaxine HCl drug contained in the functional core of the mini-tablet. As set forth in the above rejection, Mulye teaches that the low molecular weight component in his inventive coating composition, prevent rapid movement of water through the coat because of its uniformly dispersed component which allows uniform wetting of the coat and allows better adhesion to the water wettable core . As such, utilizing the coating formulation taught by Mulye, for sustained release of a drug, an ordinarily skilled artisan would essentially have a composition which limits the rapid water diffusion across the coating which consequently prevents initial rapid diffusion of the drug substance from the functional cores.

Finally, it is noted that while the Appellants have exemplified methods of preparing several different mini-tablet formulations with varying coating formulations, Appellants have failed to demonstrate any unexpected results obtained with their instantly claimed extended release mini-tab formulation of Venlafaxine HCl in comparison to the extended release spheroids of Sherman.

In view of these facts, Appellant's argument that the prior art does not suggest such a formulation is unpersuasive. It is therefore, the position of the examiner that the teachings of Sherman in combination with the teachings of Oosterbaan and Muyle suggest of teaches the subject matter of the claimed extended release formulations. The examiner maintains the argument that it would have been obvious to an artisan of ordinary skill at the time of the invention was made to substitute the spheroids of Sherman with the mini-tablets disclosed by Oosterbaan which are functionally coated as per the teachings of Sherman and Muyle to arrive at the instantly claimed formulation. One of ordinary skill in the art would have been motivated to do so because extended release formulations comprising spheroids and mini-tablets and the process of coating to provide extended release are a well established art in the pharmaceutical sciences as evidenced by Sherman, Oosterbaan and Muyle. Furthermore, one would have been motivated with a reasonable expectation of success to substitute the spheroids of Sherman with mini-tablets given the advantages of being able to deliver multiple strength dosages by preparing just one form of the drug, as suggested in Oosterbaan using the coating procedure taught by Sherman or Muyle to provide effective release of the agent.

For these reasons set forth *supra*, and those previously made of record at p.15-19 of the previous Office Action dated 04/15/2010, rejection of claims 1-7, 9-12 and 14-22 remains proper.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

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